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FACT SHEET

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This fact sheet is for use to assist in media and press-related activities. It contains information regarding INPEFA™ (sotagliflozin), a drug recently approved by the US Food and Drug Administration, including the indication, important safety information and efficacy results from the SOLOIST-WHF and other clinical studies. Recipients are encouraged to review the full **Prescribing Information** for INPEFA.

inpefa™ sotagliflozin tablets

A new option for treatment of Heart Failure (HF)

INDICATION AND KEY DATA

Approved by the U.S. Food and Drug Administration (FDA) on May 26, 2023, **INPEFA™ (sotagliflozin) is a once-daily oral tablet to reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with:**

heart failure or

type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors[1]

- INPEFA has been granted a broad label **across full range of left ventricular ejection fraction,** including HFpEF and HFrEF, and for **patients with or without diabetes.**[2]
- A third-party analysis presented at the leading international conference for health economics and outcomes research (ISPOR) in May 2023 concluded that INPEFA is a **clinically and economically attractive medication** that should be considered **a cost-effective treatment for patients with HF and diabetes** at the commonly accepted willingness-to-pay threshold.[3]
- **The SGLT inhibitor class was recommended as first-line treatment for heart failure** by the American Heart Association, the American College of Cardiology, and the Heart Failure Society of America in their joint 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure.[4]
- An April 2023 ACC expert consensus statement highlighted the benefit of SGLT inhibitors as part of Guideline-Directed Medical Therapy (GDMT) in individuals with heart failure with preserved ejection fraction (HFpEF). According to the ACC expert consensus statement, **SGLT2 inhibitors should be initiated in all individuals with HFpEF** who are stable during hospitalization and have no patient population contraindications.[5,6]

FDA approval is based on **Lexicon's two multi-center, randomized, double-blind, placebo-controlled, Phase 3 cardiovascular outcomes studies – SOLOIST-WHF and SCORED** – which included nearly 12,000 patients with HF or at risk of HF.[6,7]

INPEFA is 1 of 3 SGLT inhibitors currently indicated for heart failure

Both the **SOLOIST-WHF** and **SCORED** trials **evaluated the cardiovascular efficacy of INPEFA vs placebo** when added to standard of care, and each met their respective primary endpoints:

The total number of events, comprised of

Deaths from cardiovascular causes

Hospitalizations for HF

Urgent visits in patients with HF

Results demonstrated **overall tolerability similar to placebo.**[6,7]

Please see Pg.3 of this fact sheet for Important Safety Information (ISI)

SOLOIST–WHF included **1,222 patients** recently hospitalized for worsening HF.[6] Results showed:

INPEFA significantly **reduced risk of the composite of hospitalizations for HF,**

urgent visits for HF,

and cardiovascular death by

33%

compared to placebo

HR=0.67 (95% CI 0.53-0.85, p=0.001)

INPEFA reduced the risk of **cardiovascular death and HF rehospitalizations by greater than**

50%

at

30 days

after discharge

compared to placebo

HR=0.49 (95% CI 0.27-0.91)

Initiating **treatment with INPEFA** prior to, or within 3 days following hospital discharge

reduced the composite of **cardiovascular death** and **urgent visits for HF within**

27 days

compared to placebo

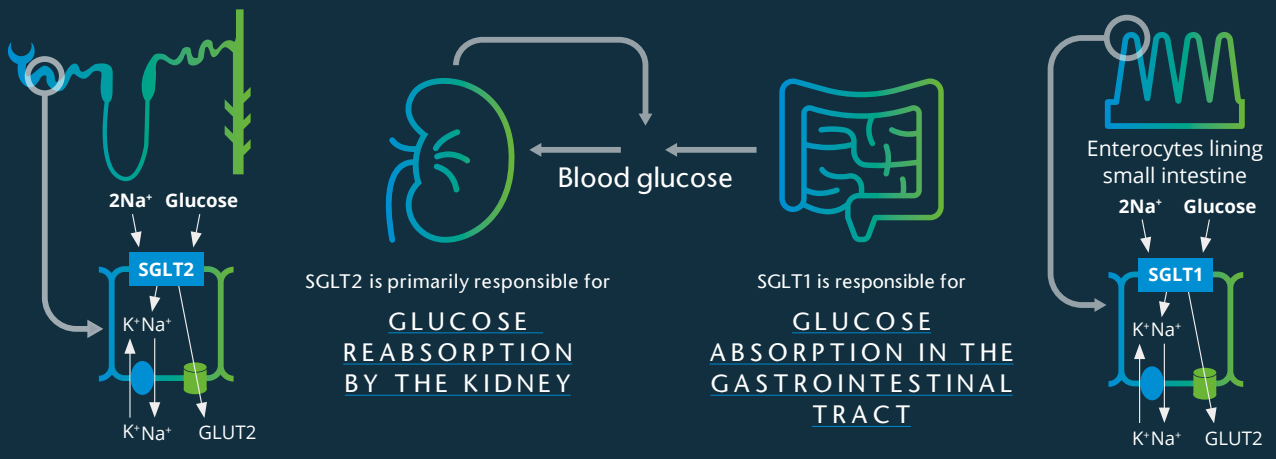
HR=0.62 (95% CI 0.39-0.99)

Most common adverse reactions (incidence ≥ 5%) of INPEFA include urinary tract infection, volume depletion, diarrhea, and hypoglycemia. Before initiating INPEFA, assess risk factors for ketoacidosis. If ketoacidosis is suspected, discontinue and treat promptly.

INPEFA has an incredibly low **NUMBER NEEDED TO TREAT (NNT) of 4** meaning **only 4 patients** would need to be treated for 1 year to avoid 1 cardiovascular event.[6]

Overall, INPEFA has been studied across **multiple patient populations** including HF, in clinical trials involving approximately **20,000 participants.**[8]

INPEFA IS AN INHIBITOR OF SGLT2 AND SGLT1[9]



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May 2023

Please see Pg.3 of this fact sheet for Important Safety Information (ISI)

inpefa™
sotagliflozin tablets

INDICATION

INPEFA is indicated to reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with:

- heart failure or
- type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors

IMPORTANT SAFETY INFORMATION

Dosing: Assess renal function and volume status and, if necessary, correct volume depletion prior to initiation of INPEFA. INPEFA dosing for patients with decompensated heart failure may begin when patients are hemodynamically stable, including when hospitalized or immediately upon discharge.

Contraindications: INPEFA is contraindicated in patients with a history of serious hypersensitivity reaction to INPEFA.

Warnings and Precautions:

- **Ketoacidosis:** INPEFA increases the risk of ketoacidosis in patients with type 1 diabetes mellitus (T1DM). Type 2 diabetes Mellitus (T2DM) and pancreatic disorders are also risk factors. The risk of ketoacidosis may be greater with higher doses. There have been postmarketing reports of fatal events of ketoacidosis in patients with type 2 diabetes using sodium glucose transporter 2 (SGLT2) inhibitors. Before initiating INPEFA, assess risk factors for ketoacidosis. Consider ketone monitoring in patients with T1DM and consider ketone monitoring in others at risk for ketoacidosis and educate patients on the signs/symptoms of ketoacidosis. Patients receiving INPEFA may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis. INPEFA is not indicated for glycemic control. Assess patients who present with signs and symptoms of metabolic acidosis or ketoacidosis, regardless of blood glucose level. If suspected, discontinue INPEFA, evaluate, and treat promptly. Monitor patients for resolution of ketoacidosis before restarting INPEFA.
- **Volume Depletion:** INPEFA can cause intravascular volume depletion which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine. There have been post-marketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors. Patients with impaired renal function (eGFR < 60 mL/min/1.73 m^2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating INPEFA in patients with one or more of these characteristics, assess volume status and renal function, and monitor for signs and symptoms of hypotension during therapy.
- **Urosepsis and Pyelonephritis:** Treatment with SGLT2 inhibitors, including INPEFA, increases the risk for urinary tract infections. Serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization have been reported. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly.
- **Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues:** Insulin and insulin secretagogues are known to cause hypoglycemia. INPEFA may increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used with INPEFA.
- **Necrotizing Fasciitis of the Perineum (Fournier's Gangrene):** Reports of Fournier's Gangrene, a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in post-marketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors. Assess patients who present with pain, tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue INPEFA, closely monitor patient signs and symptoms, and provide appropriate alternative therapy for heart failure.
- **Genital Mycotic Infections:** INPEFA increases the risk of genital mycotic infections. Monitor and treat as appropriate.
- **Urinary Glucose Test and 1,5-anhydroglucitol (1,5-AG) Assay:** These are not reliable for patients taking SGLT2 inhibitors. Use alternative testing methods to monitor glucose levels.

Common Adverse Reactions: the most commonly reported adverse reactions (incidence ≥ 5%) were urinary tract infection, volume depletion, diarrhea, and hypoglycemia.

Drug Interactions:

- **Digoxin:** Monitor patients appropriately as there is an increase in the exposure of digoxin when coadministered with INPEFA 400 mg.
- **Uridine 5'-diphospho-glucuronosyltransferase (UGT) Inducer:** The coadministration of rifampicin, an inducer of UGTs, with sotagliflozin resulted in a decrease in the exposure of sotagliflozin.
- **Lithium:** Concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations. Monitor serum lithium concentration more frequently during INPEFA initiation and with dosage changes.

Use in Specific Populations:

- **Pregnancy and Lactation:** INPEFA is not recommended during the second and third trimesters of pregnancy, nor while breastfeeding.
- **Geriatric Use:** No INPEFA dosage change is recommended based on age. No overall differences in efficacy were detected between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Elderly patients may be at increased risk for volume depletion adverse reactions, including hypotension.
- **Renal Impairment:** INPEFA was evaluated in patients with chronic kidney disease (eGFR 25 to 60 mL/min/1.73 m^2) and in patients with heart failure with eGFR < 60 mL/min/1.73 m^2. The safety profile of INPEFA across eGFR subgroups in these studies was consistent with the known safety profile. There was an increase in volume-related adverse events (e.g., hypotension, dizziness) in patients with eGFR < 30 mL/min/1.73m^2 relative to the overall safety population. Efficacy and safety studies with INPEFA did not enroll patients with an eGFR less than 25 mL/min/1.73 m^2 or on dialysis. After starting therapy in the studies, patients were discontinued if eGFR fell below 15 mL/min/1.73 m^2 or were initiated on chronic dialysis.
- **Hepatic Impairment:** INPEFA is not recommended in patients with moderate or severe hepatic impairment.

For more information, see full Prescribing Information.
https://www.lexpharma.com/inpefa-US-PI.pdf

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REFERENCE: **1.** INPEFA [prescribing information]. Lexicon Pharmaceuticals, Inc.; May 2023.

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FACT SHEET

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Heart Failure (HF)
A debilitating disease with great unmet medical need

More than 20 years ago, the authors of a study assessing HF survival in patients 67 years or older said, "Survival following a diagnosis of HF is bleak and may be worse than the prognosis for most types of cancer." [1]

~6.7 million US HF prevalence in 2019.[2]

8 million estimated US HF prevalence by 2030.[2]

#1 cause of hospitalizations for Americans aged 65+.[3,4]

1.3 million hospitalizations for HF annually in the US.[2]

Many advances later, HF remains an area of great unmet medical need.[3] It is a debilitating disease that continues to significantly impact those who are diagnosed and their loved ones.

WHAT IS HF?

- HF occurs when the heart cannot pump enough blood and oxygen to support other organs in the body that depend on the heart to deliver oxygen and nutrient-rich blood to cells.[5,6]
- Acute HF can develop suddenly.[5,6]
- HF often results in fatigue and shortness of breath, making everyday activities difficult.[5,6]
- Chronic HF is a progressive condition that develops as the heart gets weaker, meaning the heart is not pumping blood as well as it should and is no longer able to function and circulate blood efficiently.[5,6]
- Patients with severe HF can become incapacitated due to fluid build-up, creating a disturbing sensation of drowning, and require hospitalization.[7]

RISK FACTORS THAT IMPACT THE COURSE OF HF:[6]

Diagnosis with multiple comorbidities, including diabetes mellitus, chronic kidney disease (CKD), peripheral vascular disease, and stroke.

Personal or family **history of HF.**

Heart or blood vessel conditions, serious lung diseases, HIV, SARS-CoV-2, and other infections.

Unhealthy lifestyle habits, such as smoking, diet, drug and alcohol use, lack of physical activity.

Age - people 65 years and older have a higher rate of HF.

Race - Black and African Americans are more likely to have HF than people of other races, often developing more serious cases of the disease and at a younger age.

CAUSES AND TYPES OF HF

HF is usually caused by **another disease** that damages the heart, such as coronary heart disease, heart attack, inflammation of the heart, high blood pressure, cardiomyopathy or an irregular heartbeat.[6,8]

HF with **preserved ejection fraction** (HFpEF), also called **diastolic HF**, is when the left ventricle has a problem filling with blood.[9]

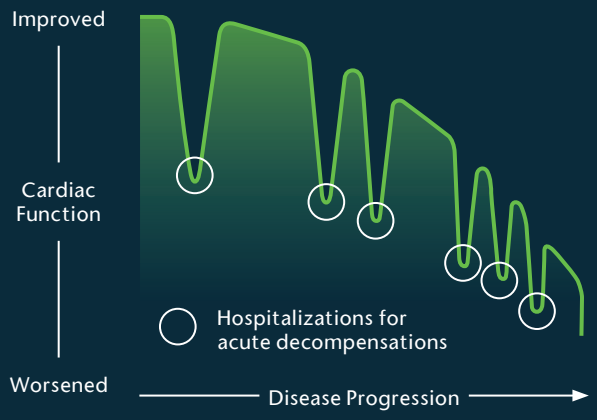
HF with **reduced ejection fraction** (HFrEF), also called **systolic HF**, means the left ventricle isn't strong enough to pump enough blood to the body.[9]

HF IS OFTEN MARKED WITH ACUTE EPISODES OF REDUCED CARDIAC FUNCTION THAT REQUIRE IN-PATIENT CARE AT A HOSPITAL[10-12]

THE TYPICAL TRAJECTORY OF WORSENING HF[11]

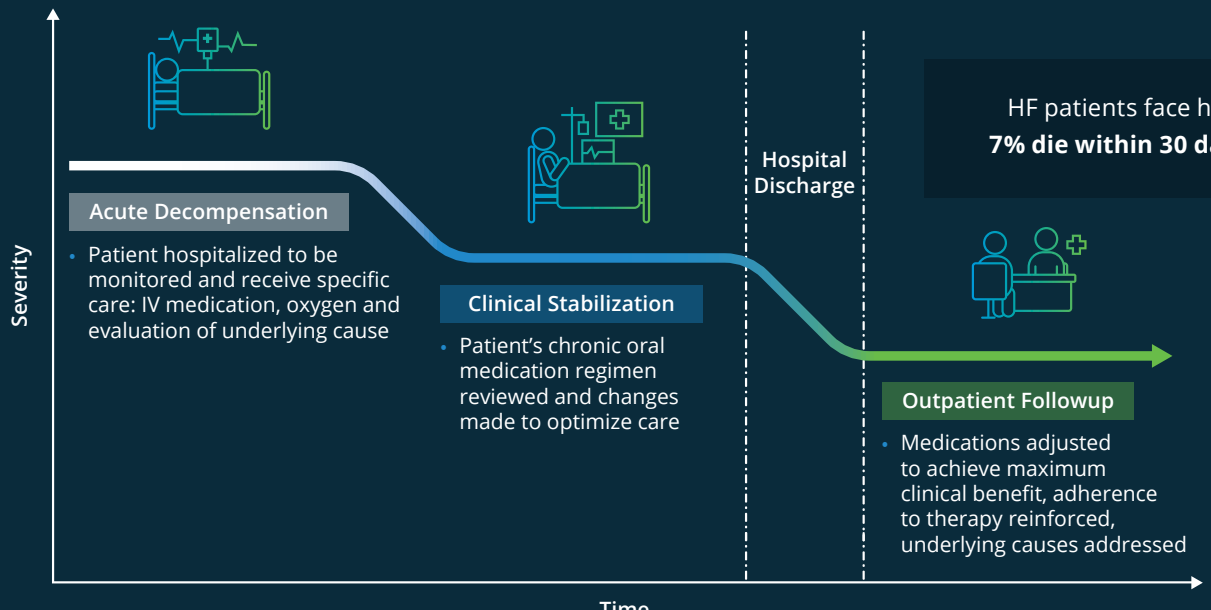
If the patient's condition declines, worsening HF **often requires rehospitalizations** and escalation of therapy.[10-12]

Hospitalizations for acute decompensation are illustrated as a sharp decline in cardiac function along disease progression.



30 DAYS - A CRITICAL TIME

Patients with HF are often caught in a cyclical pattern of rehospitalizations, with nearly **25% readmitted within only 30 days of discharge.**[13]



HF patients face high mortality rates – **7% die within 30 days post-discharge.**[14]

Figure adapted from Ferro et al.[15]

PERSONAL, ECONOMIC AND SOCIETAL BURDENS OF HF IN THE US ARE SIGNIFICANT

The annual cost of hospitalizations and readmissions driving the majority of HF-related expenditures in 2020 was **$43 billion**.[10]

Annual costs of HF are expected to increase to nearly **$70 billion by 2030**, with 80% of those costs due to hospitalizations.[10]

On top of the burden for patients, each time someone with HF is re-hospitalized, it costs the healthcare system an estimated **$15K-$26K**.[16]

Patients, their families, and loved ones, especially those who are caregivers, have **added stress** and responsibility due to initial hospitalizations and the cyclical pattern of readmissions.[17-19]

65% of patients are rehospitalized within one year; recurrent hospitalizations after discharge are common, costly, and often preventable.[10]

50% of patients die within 5 years of diagnosis.[10]

There is no cure for HF, but healthy lifestyle changes, some medical devices and procedures, and an increasing number of safe and effective medicines, can help many people have an improved quality of life.[6,8]

NEW TREATMENT GUIDELINES

- The newest class of FDA-approved medicines for prevention and treatment of HF are sodium-glucose cotransporter inhibitors - types 2 and 1 (SGLT2 and SGLT1) – that inhibit two proteins responsible for glucose regulation. SGLT2 is primarily responsible for glucose reabsorption by the kidney and SGLT1 is responsible for glucose absorption in the gastrointestinal tract.[20]
- The SGLT inhibitor class was recommended as first-line treatment for HF by the American Heart Association, the American College of Cardiology, and the Heart Failure Society of America in their joint 2022 AHA/ACC/HFSA Guideline for the Management of HF.[21]
- An April 2023 American College of Cardiology expert consensus statement highlighted the benefit of the SGLT inhibitor class of medicines as part of Guideline-Directed Medical Therapy (GDMT) in individuals with HF with preserved ejection fraction (HFpEF). According to the ACC expert consensus statement, SGLT2 inhibitors should be initiated in all individuals with HFpEF who are stable during hospitalization and have no patient population contraindications.[22]
- As recently as 2022, more than 40% of hospitalized HF patients were not started on an SGLT inhibitor or other guideline-directed treatments within 30 days after discharge. [21,23]

Contact us **corpcomm@lexpharma.com** 2445 Technology Forest Blvd. 11th Floor, The Woodlands, TX 77381

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Lexicon pharmaceuticals

May 2023

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FACT SHEET

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This fact sheet is for use to assist in media and press-related activities. It contains information regarding INPEFA™ (sotagliflozin), a drug recently approved by the US Food and Drug Administration, including the indication, important safety information and efficacy results from the SOLOIST-WHF and other clinical studies. Recipients are encouraged to review the full **Prescribing Information** for INPEFA.

Lexicon is a biopharmaceutical company with a mission of pioneering medicines that transform patients' lives.

With a unique application of gene science, Lexicon discovers and develops innovative and precise medicines to provide new treatment options for people with serious, chronic conditions.

Precision Science:

Through our **Genome5000™** program, Lexicon scientists studied the role and function in mammalian physiology and behavior of nearly **5,000 genes** to pinpoint key targets for drug development.

Pioneering Medicines:

Lexicon's passion is to bring **innovative new medicines** to the market that have the **potential to substantially improve the standard of care**. We maintain a diverse portfolio of targets and discovery and development programs with a focus on cardiometabolism and neuroscience.

Patient Driven:

We believe in treating people, not just diseases. Our goal is to generate **solutions for patients** that will make meaningful, long-term improvements in their lives.

TAKING FLIGHT - OUR STORY

1. Lexicon was conceived to **understand the functions of genes in mammalian physiology and behavior,** advancing from the foundational discoveries of **the Human Genome Project.**

2. **Lexicon's 10 yr Genome5000™ project** systematically defined the **functions of approximately 5,000 genes.**

3. Providing us with a **unique perspective** and **understanding of potential therapeutic targets,** enabling genetically-informed drug discovery with an **opportunity to open new frontiers in medicine.**

100 proteins with significant therapeutic potential across a range of diseases.

4. We are one of a small number of companies to have brought a drug to market from our own laboratories.

5. We **are commercializing INPEFA™ (sotagliflozin), an inhibitor of SGLT2 and SGLT1 for the treatment of heart failure.**

6. **Our unique discovery to commercialization pipeline continues to generate unique assets** across diverse therapeutic areas, including a **novel non-opioid investigational approach to neuropathic pain, LX9211.**

As Lexicon continues to evolve, we remain steadfast in our mission to bring new therapeutic solutions to patients in need.

inpefa™
sotagliflozin tablets

2023 - A TRANSFORMATIVE YEAR FOR LEXICON: FDA APPROVAL OF INPEFA™ (SOTAGLIFLOZIN) FOR PATIENTS WITH HEART FAILURE (HF)

Approved by the U.S. Food and Drug Administration (FDA) on May 26, 2023, **INPEFA is a once-daily oral tablet to reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with:**

- **heart failure or**
- **type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors** [1,2]

INPEFA has been granted a broad label **across full range of left ventricular ejection fraction,** including HFpEF and HFrEF, and for **patients with or without diabetes.**[2]

INPEFA inhibits both sodium-glucose cotransporter type 2 (SGLT2) and type 1 (SGLT1). SGLT2 is responsible for glucose reabsorption by the kidney and SGLT1 is responsible for glucose absorption in the gastrointestinal tract.[3-5]

The SGLT inhibitor class was recommended as first-line treatment for heart failure by the American Heart Association, the American College of Cardiology, and the Heart Failure Society of America in their joint 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure.[6]

RESULTS FROM SOLOIST-WHF SHOWED:[7]

INPEFA significantly **reduced risk of the composite of hospitalizations for HF,**

urgent visits for HF,

and cardiovascular death by

33%

compared to placebo

HR=0.67 (95% CI 0.53-0.85, p=0.001)

INPEFA reduced the risk of **cardiovascular death and HF rehospitalizations by greater than**

50%

at

30 days

after discharge

compared to placebo

HR=0.49 (95% CI 0.27-0.91)

Initiating **treatment with INPEFA** prior to, or within 3 days following hospital discharge

reduced the composite of **cardiovascular death** and **urgent visits for HF within**

27 days

compared to placebo

HR=0.62 (95% CI 0.39-0.99)

Most common adverse reactions (incidence ≥ 5%) of INPEFA include urinary tract infection, volume depletion, diarrhea, and hypoglycemia. Before initiating INPEFA, assess risk factors for ketoacidosis. If ketoacidosis is suspected, discontinue and treat promptly.

Please see Pg.4 of this fact sheet for Important Safety Information (ISI)

2023 - A TRANSFORMATIVE YEAR FOR LEXICON: ADVANCING AN INNOVATIVE APPROACH TO TREAT NEUROPATHIC PAIN

Planning is under way for advancing the clinical program for LX9211. It is a novel, opioid-free, investigational medicine to treat peripheral neuropathic pain, a serious and often debilitating condition that affects more than 40 million people in the U.S.[8,9]

Neuropathic pain is associated with several medical conditions, including Diabetic Peripheral Neuropathic Pain (DPN), a common complication of diabetes.[10]

For most patients, the current standard of care often results in undesirable side effects and does not eliminate neuropathic pain; this is an area of large unmet medical need.[12,13]

LX9211 has potential to be the first major drug innovation in many years for a large, poorly served patient population.

LX9211 has received Fast-Track designation from the U.S. Food and Drug Administration for development in DPN.[13]

15+

years of research and development provides evidence that:[8-12]

This unique target avoids the opioid pathway

Clinical data support once-daily dosing

WE COMPLETED TWO PHASE 2 CLINICAL TRIALS OF LX9211 IN NEUROPATHIC PAIN IN 2022[14]

COMPLETE

RELIEF-DPN-1

in patients with diabetic peripheral neuropathic pain

COMPLETE

RELIEF-PHN-1

in patients with postherpetic neuralgia (PHN)

Planned advancement of LX9211 into **late-stage development** in neuropathic pain

References: 1. U.S. Food and Drug Administration. Novel Drug Approvals for 2023 [Internet] 2023 [cited May 2023]: https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2023 **2.** Lexicon Pharmaceuticals. Inpefa USA Prescribing Information [Internet] 2023 [cited May 2023] https://www.lexpharma.com/inpefa-US-PI.pdf **3.** Vallianou NG et al. Sotagliflozin, a dual SGLT1 and SGLT2 inhibitor: In the heart of the problem. Metabol Open. 2021;10:100089 **4.** Data on file. Lexicon 2022 **5.** Pitt B, Bhatt DL. Does SGLT1 Inhibition Add Benefit to SGLT2 Inhibition in Type 2 Diabetes? Circulation. 2021;144(1):4-6 **6.** Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines [published correction appears in Circulation. 2022 May 3;145(18):e1033]. Circulation. 2022;145(18):e895-e1032. doi: 10.1161/CIR.0000000000001063 **7.** Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. N Engl J Med. 2021;384(2):117-128. https://www.nejm.org/doi/full/10.1056/NEJMoa2030183 **8.** Kostich W, Hamman BD, Li YW, et al. Inhibition of AAK1 Kinase as a Novel Therapeutic Approach to Treat Neuropathic Pain. J Pharmacol Exp Ther. 2016;358(3):371-386. doi:10.1124/jpet.116.235333 **9.** Massachusetts General Hospital. Neuropathy Overview. [Internet] 2021 [cited May 2023] Available from: https://neuropathycommons.org/neuropathy/neuropathy-overview **10.** Schreiber AK, Nones CF, Reis RC et al. Diabetic neuropathic pain: Physiopathology and treatment. World J Diabetes. 2015;6(3):432-444. doi:10.4239/wjd.v6.i3.432 **11.** Schembri, E. Are Opioids Effective in Relieving Neuropathic Pain? SN Compr. Clin. Med. 1, 30–46 (2019). https://doi.org/10.1007/s42399-018-0009-4. **12.** Bundrant L, Hunt TL, Banks P,et al. Results of two Phase 1, Randomized, Double-blind, Placebo-controlled, Studies (Ascending Single-dose and Multiple-dose Studies) to Determine the Safety, Tolerability, and Pharmacokinetics of Orally Administered LX9211 in Healthy Participants. Clin Ther. 2021;43(6):1029-1050. doi:10.1016/j.clinthera.2021.04.014 **13.** Lexicon Pharmaceuticals receives fast track designation from the FDA for LX9211 for diabetic peripheral neuropathic pain. Nasdaq. December 11, 2020. Accessed May 12, 2023. https://www.nasdaq.com/press-release/lexicon-pharmaceuticals-receives-fast-track-designation-from-the-fda-for-lx9211-for. **14.** RELIEF-DPN 1 and RELIEF-PHN 1 clinical trial data on file with Lexicon, 2022

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May 2023

inpefa™
sotagliflozin tablets

INDICATION

INPEFA is indicated to reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with:

- heart failure or
- type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors

IMPORTANT SAFETY INFORMATION

Dosing: Assess renal function and volume status and, if necessary, correct volume depletion prior to initiation of INPEFA. INPEFA dosing for patients with decompensated heart failure may begin when patients are hemodynamically stable, including when hospitalized or immediately upon discharge.

Contraindications: INPEFA is contraindicated in patients with a history of serious hypersensitivity reaction to INPEFA.

Warnings and Precautions:

- **Ketoacidosis:** INPEFA increases the risk of ketoacidosis in patients with type 1 diabetes mellitus (T1DM). Type 2 diabetes Mellitus (T2DM) and pancreatic disorders are also risk factors. The risk of ketoacidosis may be greater with higher doses. There have been postmarketing reports of fatal events of ketoacidosis in patients with type 2 diabetes using sodium glucose transporter 2 (SGLT2) inhibitors. Before initiating INPEFA, assess risk factors for ketoacidosis. Consider ketone monitoring in patients with T1DM and consider ketone monitoring in others at risk for ketoacidosis and educate patients on the signs/symptoms of ketoacidosis. Patients receiving INPEFA may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis. INPEFA is not indicated for glycemic control. Assess patients who present with signs and symptoms of metabolic acidosis or ketoacidosis, regardless of blood glucose level. If suspected, discontinue INPEFA, evaluate, and treat promptly. Monitor patients for resolution of ketoacidosis before restarting INPEFA.
- **Volume Depletion:** INPEFA can cause intravascular volume depletion which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine. There have been post-marketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors. Patients with impaired renal function (eGFR < 60 mL/min/1.73 m^2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating INPEFA in patients with one or more of these characteristics, assess volume status and renal function, and monitor for signs and symptoms of hypotension during therapy.
- **Urosepsis and Pyelonephritis:** Treatment with SGLT2 inhibitors, including INPEFA, increases the risk for urinary tract infections. Serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization have been reported. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly.
- **Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues:** Insulin and insulin secretagogues are known to cause hypoglycemia. INPEFA may increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used with INPEFA.
- **Necrotizing Fasciitis of the Perineum (Fournier's Gangrene):** Reports of Fournier's Gangrene, a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in post-marketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors. Assess patients who present with pain, tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue INPEFA, closely monitor patient signs and symptoms, and provide appropriate alternative therapy for heart failure.
- **Genital Mycotic Infections:** INPEFA increases the risk of genital mycotic infections. Monitor and treat as appropriate.
- **Urinary Glucose Test and 1,5-anhydroglucitol (1,5-AG) Assay:** These are not reliable for patients taking SGLT2 inhibitors. Use alternative testing methods to monitor glucose levels.

Common Adverse Reactions: the most commonly reported adverse reactions (incidence ≥ 5%) were urinary tract infection, volume depletion, diarrhea, and hypoglycemia.

Drug Interactions:

- **Digoxin:** Monitor patients appropriately as there is an increase in the exposure of digoxin when coadministered with INPEFA 400 mg.
- **Uridine 5'-diphospho-glucuronosyltransferase (UGT) Inducer:** The coadministration of rifampicin, an inducer of UGTs, with sotagliflozin resulted in a decrease in the exposure of sotagliflozin.
- **Lithium:** Concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations. Monitor serum lithium concentration more frequently during INPEFA initiation and with dosage changes.

Use in Specific Populations:

- **Pregnancy and Lactation:** INPEFA is not recommended during the second and third trimesters of pregnancy, nor while breastfeeding.
- **Geriatric Use:** No INPEFA dosage change is recommended based on age. No overall differences in efficacy were detected between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Elderly patients may be at increased risk for volume depletion adverse reactions, including hypotension.
- **Renal Impairment:** INPEFA was evaluated in patients with chronic kidney disease (eGFR 25 to 60 mL/min/1.73 m^2) and in patients with heart failure with eGFR < 60 mL/min/1.73 m^2. The safety profile of INPEFA across eGFR subgroups in these studies was consistent with the known safety profile. There was an increase in volume-related adverse events (e.g., hypotension, dizziness) in patients with eGFR < 30 mL/min/1.73m^2 relative to the overall safety population. Efficacy and safety studies with INPEFA did not enroll patients with an eGFR less than 25 mL/min/1.73 m^2 or on dialysis. After starting therapy in the studies, patients were discontinued if eGFR fell below 15 mL/min/1.73 m^2 or were initiated on chronic dialysis.
- **Hepatic Impairment:** INPEFA is not recommended in patients with moderate or severe hepatic impairment.

For more information, see full Prescribing Information.
https://www.lexpharma.com/inpefa-US-PI.pdf

Lexicon pharmaceuticals

REFERENCE: **1.** INPEFA [prescribing information]. Lexicon Pharmaceuticals, Inc.; May 2023.